REMARKS

Upon entry of the present amendments, claims 32-42 are pending. Claims 1, 4, 5, 11, 13, 14, 20, 21 and 31 have been canceled, without prejudice. The Examiner's bases for rejecting claims 1, 4, 5, 11, 13, 14, 20, 21 and 31 are addressed below. The foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lesser, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

The Specification was amended to correct a clerical error; lines 30-31 of page 1 were deleted, as these two lines were duplicates of lines 1-2 of page 2. The Specification was further amended at page 5 to insert language proposed by the Examiner. the Examiner stated that no drawings or figures were submitted with the instant disclosure. Finally, as suggested by the Examiner, Applicants have submitted the three figures in the original PCT application (PCT/FR98/00081) herewith, and have amended the Specification to insert a brief description of the drawings. Support for the description of figures 1 and 2 can be found at Specification page 12, lines 6-22; and support for the description of figure 3 can be found at Specification page 12, lines 23-28.

New claims 32-42 are supported by canceled claims 1, 4, 5, 11, 13, 14, 20, 21 and 31 and the specification, as follows:

New claim 32 is supported by canceled claim 21 and Specification page 5, lines 5-18, as amended herein; page 8, lines 3-9; and page 15, lines 15-22. New claim 33 is supported by canceled claim 1. New claims 34 and 41 are supported by Specification FIG. 3. New claims 35, 36, 37, 38, and 39 are supported by canceled claims 4, 5, 11, 13, and 14. New claims 40 and 42 are supported by canceled claims 20 and 31, and Specification page 5, lines 5-18, as amended herein.

Pursuant to 37 CFR 1.121(b)(1)(iii), a marked up version of the amended claims showing the changes made is attached hereto. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

CLAIM OBJECTIONS

The Examiner has objected to claims 20 and 31, stating that the claims have various informalities. Applicants have cancelled claims 20 and 31 and made the appropriate corrections in corresponding claims 40 and 42. Thus, the present objections are now moot. Accordingly, Applicants request withdrawal of the claim objections.

SPECIFICATION

The Examiner has objected to the Specification because of the following informalities:

First, the Examiner stated that no drawings or figures were submitted with the instant disclosure. The Examiner noted that the original PCT application, PCT/FR98/00081, contained three figures, but that both the instant disclosure and the PCT application did not indicate that a brief description of the drawings is present. The Examiner then stated that if drawings were submitted, appropriate correction would be required. See, April 10, 2002 Office Action at page 3. Applicants have submitted the three figures herewith, and have amended the Specification to insert a brief description of the drawings.

Second, the Examiner has alleged that the passage at page 5, lines 7-8 of the Specification has translation errors and has provided a "more literal and proper translation of the passage" at page 4 of April 10, 2002 Office Action. In order to expedite prosecution of the present application, Applicants have amended the Specification to incorporate the translation of the passage proposed by the Examiner.

In view of the above-described amendments, Applicants respectfully request reconsideration and withdrawal of these objections.

SEQUENCE COMPLIANCE

The Examiner has stated that if the drawings from PCT/FR98/00081 are submitted, then Applicants must comply with 37 CFR 1.821-1.825, as figures 1 and 2 contain polynucleotide sequences. Applicants have submitted figures 1 and 2 herewith and, accordingly, a Sequence Listing is submitted herewith in order to comply with 37 CFR 1.821-1.825.

35 U.S.C. § 112, FIRST PARAGRAPH REJECTION

The Examiner has maintained the rejection of claims 1, 4, 5, 11, 13, 14, 20, 21, and 31 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the Specification. Specifically, the Examiner has alleged that claims 1 and 20 are indefinite in their recitation of the phrase "signal peptide" and claims 21 and 31 are indefinite in their recitation of the phrase "a sequence ... permitting the secretion of said antibody." The Examiner states that, in both cases, "the claims clearly make reference to signal peptide sequences." In response to Applicants' previous argument that signal peptides are disclosed in Figures 1 and 2 of the Specification, the Examiner asserts that:

> ∴ the mere presence of an element in a figure illustrating a cloned sequence would not support the general use of attaching this particular element or the whole genus of these elements. A close review of the instant specification indicates that the antibody produced in the example is secreted, **however, there is no clear indication or recitation in the present disclosure that this is a critical or necessary element which was specifically contemplated.**

Emphasis added. *See* April 10, 2002 Office Action at pages 6-7.

Applicants traverse and strongly disagree with the Examiner's assertions. The instant Specification provides clear indication that a sequence permitting the secretion of said antibody is a critical element of the present invention. For example, the Specification clearly states:

> As a result, the present invention concerns a biological material for preparing a pharmaceutical composition for treating a mammal by gene transfer...
>
> The biological material is characterized by the fact that said nucleic acid sequence contains an antibody gene and **elements guaranteeing** the *in vivo* expression of said antibody gene and **the secretion in the blood circulation of a mammal of a therapeutically effective amount of this antibody or a fragment of it, by cells of said mammal genetically modified by said nucleic acid sequence** and not naturally producing antibodies.

Emphasis added. *See,* Specification at page 4, line 17 through page 5, line 2. Indeed, the Specification is replete with such teachings. Additional examples of such teachings can be found at, for example, Specification page 5, lines 23-28; page 6, lines 7-12; page 6, lines 15-20; page 7, lines 1-7; page 10, lines 16-20; page 11, lines 1-6; and claims 1-4, 6, 16, 18, and 20, as originally filed. Thus, in contrast to the Examiner's assertions, Applicants respectfully submit that there is clear and ample indication in the disclosure that a nucleic acid sequence for the secretion of the

antibody (*i.e.*, a signal peptide) is a critical and necessary element of the present invention. Moreover, nucleic acid sequences enabling the secretion of proteins (*i.e.*, signal peptides) were well known in the art at the time of filing of the present invention. Indeed, as reviewed in the biochemistry textbook Stryer (see copy of passage attached herewith), the signal sequence hypothesis dates back to 1970, and signal sequences of many proteins were known by the early 1980s. Stryer, BIOCHEMISTRY, 2ND ED. (W.H Freeman and Company, New York, San Francisco, 1981), pp. 713-714. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

35 U.S.C. § 112, SECOND PARAGRAPH REJECTION

The Examiner has rejected claims 1, 11, 20, 21, and 31 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner has stated that claims 1 and 20 are vague and unclear in the recitation of "natural antibody polypeptide." This rejection is moot in light of the cancellation of claims 1 and 20 by the present amendment. New claims 32-42 do not recite the term "natural antibody polypeptide." Rather, the new claims recite the term "native, unmodified antibody molecule," a term suggested by the Examiner and supported at Specification page 5, lines 5-13, as amended herein. Accordingly, Applicants respectfully request reconsideration and withdrawal of this present rejection.

The Examiner also stated that claim 11 is "unclear and confusing in the recitation of 'hematopoietic cells' because the instant invention as set forth in the independent claim is drawn to using non-plasmacyte cells." The Examiner alleges that "[a] **plasmacyte is not specifically defined in the specification**, however the art definition encompasses cells present in the plasma." *See,* April 10, 2002 Office Action at page 11.

Applicants traverse and strongly disagree with the Examiner's allegations. The Specification clearly describes plasmacytes as cells specialized for antibody production. This

definition is consistent with definitions in the prior art. For example, the 1995 CD-ROM version of Stedman's Medical Dictionary provides the following definition:

> plasma cell,
> plasmacyte;
> an ovoid cell with an eccentric nucleus having chromatin arranged like a clock face or spokes of a wheel; the cytoplasm is strongly basophilic because of the abundant RNA in its endoplasmic reticulum; **plasma cell's are derived from B type lymphocytes and are active in the formation of antibodies**. [Emphasis added.]

The Specification further explains why plasmacytes are poor candidates for the long-term production of therapeutic antibodies through gene transfer and explains the importance of demonstrating that cell types not specialized for the natural production of antibodies (*i.e.*, non-plasmacytes) are capable of accepting a gene transfer, expressing a therapeutic antibody *in vivo*, and secreting sustained levels of antibodies. *See, e.g.*, Specification page 4, lines 7-16; and page 10, lines 16-20. Hematopoietic cells are not specialized for the natural production of antibodies and are thus non-plasmacytes. This rejection is moot in light of the cancellation of claim 11 by the present amendment. However, corresponding new claim 36 does recite the term "hematopoietic cells." Accordingly, Applicants respectfully submit that the recitation of "hematopoietic cells" is not "unclear and confusing" and request reconsideration and withdrawal of this rejection.

The Examiner has further stated that claims 21 and 31 are "unclear and confusing in the recitation of 'a sequence for termination of the transcription, situated downstream from the sequence coding for an antibody molecule and permitting the secretion of said antibody molecule' because there is no nexus between signals which terminate transcription and signals for secretion of a polypeptide." This rejection is moot in light of the cancellation of claims 21 and 31 by the present amendment. Moreover, corresponding new claims 32 and 42 make it clear that the termination sequence and the sequence permitting secretion are two separate sequences. Basis for this amendment can be found at, for example, Specification page 5, lines 5-18. Accordingly, Applicants respectfully request reconsideration and withdrawal of this present rejection.

35 U.S.C. § 102(B) REJECTION (WRIGHT ET AL.)

Claims 1, 4, 11, 13, 14, 20, and 21 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wright *et al.*, (Crit. Rev. Immunol., 12(3,4):125-168, 1992) (*Wright*). Applicants respectfully traverse.

This rejection is now moot in light of the cancellation of claims 1, 4, 11, 13, 14, 20, and 21 by the present amendment. However, Applicants respectfully submit that corresponding new claims 32-39 are not anticipated by *Wright*. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991).

Wright does not disclose the present invention, as claimed herein. *Wright* is a review article that explains the optimisation of the *in vitro* production of monoclonal antibodies and their purification from culture supernatants. The Examiner underlines section 6 of the review article (pp. 130-131) where the review article mentions the possibility of producing monoclonal antibodies in non-lymphoid cells. *See* April 10, 2002 Office Action at page 12. However, a careful reading of this section clearly indicates that only *in vitro* production of monoclonal antibodies is contemplated, as the authors discuss scale-up and the possibility of using serum-free media culture to facilitate antibody purification because this media is less complex. Furthermore, the non-lymphoid cells mentioned in that section are transformed cell lines (*e.g.*, C6 glioma, PC12 pheochromocytoma, HeLa and CHO). Applicants respectfully submit that a skilled artisan would not consider such tumour cells to be suitable for administration to a mammal for *in vivo* production of monoclonal antibodies, or suitable for remaining in the mammal for several months, two important characteristics taught by the Specification (*see, e.g.*, Specification at page 8, lines 3-9) and required by the new claims 32-39.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 102(B) REJECTION (STEVENSON ET AL.)

Claims 1, 4, 11, 13, 20, and 21 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Stevenson *et al.*, (Ann. N.Y. Acad. Sci., 772:212-226, 1995) (*Stevenson*). Applicants respectfully traverse.

This rejection is now moot in light of the cancellation of claims 1, 4, 11, 13, 20, and 21 by the present amendment. However, Applicants respectfully submit that corresponding new claims 32-39 are not anticipated by *Stevenson*. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991).

Stevenson does not disclose non-plasmocyte cells genetically modified with a nucleic acid sequence coding for a native, unmodified antibody, as required by new claims 32-39. The disclosure of *Stevenson* concerns only the teaching of chimeric antibodies constructed with nucleic acid coding **ScFv fragments**. In contrast, as clearly stated in the translated passage provided by the Examiner, the nucleic acid sequence in the composition of the present invention includes at least one therapeutic antibody gene which can be (1) a gene coding for a native, unmodified antibody therefore natural, **or** (2) an antibody fragment, such as Fab or $F(ab)_2$ or ScFv fragments, **or** (3) an antibody derivative such as a chimerical antibody or antibody or antibody fragment fused to an effector substance such as a toxin or hormone. *See,* Specification at page 5, lines 5-13. Since new claims 32-39 are drawn to non-plasmocyte cells genetically modified with a nucleic acid sequence coding for **a native, unmodified antibody**, *Stevenson* does not anticipate the present invention, as claimed herein.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

35 U.S.C. § 102(B) REJECTION (CHEN ET AL. (1994))

Claims 1, 4, 5, 11, 14, 20, 21, and 31 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Chen *et al.*, (Proc. Natl. Acad. Sci. USA, 91:5932-5936, 1994) (*Chen I*). Applicants respectfully traverse.

This rejection is now moot in light of the cancellation of claims 1, 4, 5, 11, 14, 20, 21, and 31 by the present amendment. However, Applicants respectfully submit that corresponding new claims 32-39, and 42 are not anticipated by *Chen I.* Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991).

Chen I does not disclose non-plasmocyte cells genetically modified with a nucleic acid sequence coding for a native, unmodified antibody, as required by the new claims 32-39, and 42. *Chen I* only teaches cells constructed with nucleic acid coding **Fab fragments**. In contrast, as clearly stated in the translated passage provided by the Examiner, the nucleic acid sequence in the composition of the present invention includes at least one therapeutic antibody gene which can be (1) a gene coding for a native, unmodified antibody therefore natural, **or** (2) an antibody fragment, such as Fab or $F(ab)_2$ or ScFv fragments, **or** (3) an antibody derivative such as a chimerical antibody or antibody or antibody fragment fused to an effector substance such as a toxin or hormone. *See,* Specification at page 5, lines 5-13. Since new claims 32-39 are drawn to non-plasmocyte cells genetically modified with a nucleic acid sequence coding for **a native, unmodified antibody**, *Chen I* does not anticipate the present invention, as claimed herein.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

35 U.S.C. § 102(B) REJECTION (CHEN ET AL. (1996))

Claims 1, 4, 5, 11, 14, 20, 21, and 31 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Chen *et al.*, (Hum. Gene Ther., 7:1515-1525, 8/1996) (*Chen II*). Applicants respectfully traverse.

This rejection is now moot in light of the cancellation of claims 1, 4, 5, 11, 14, 20, 21, and 31 by the present amendment. However, Applicants respectfully submit that corresponding new claims 32-39, and 42 are not anticipated by *Chen II*. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991).

Chen II does not disclose non-plasmocyte cells genetically modified with a nucleic acid sequence coding for a native, unmodified antibody, as required by the new claims 32-39, and 42. *Chen II* only teaches cells constructed with nucleic acid coding **Fab fragments**. In contrast, as clearly stated in the translated passage provided by the Examiner, the nucleic acid sequence in the composition of the present invention includes at least one therapeutic antibody gene which can be (1) a gene coding for a native, unmodified antibody therefore natural, **or** (2) an antibody fragment, such as Fab or $F(ab)_2$ or ScFv fragments, **or** (3) an antibody derivative such as a chimerical antibody or antibody or antibody fragment fused to an effector substance such as a toxin or hormone. *See,* Specification at page 5, lines 5-13. Since new claims 32-39 are drawn to non-plasmocyte cells genetically modified with a nucleic acid sequence coding for **a native, unmodified antibody**, *Chen II* does not anticipate the present invention, as claimed herein.

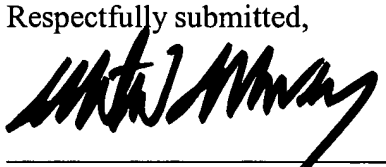
Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

August 8, 2002



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 1, please delete lines 30-31, as follows:

[The first consists of introducing the DNA sequence carrying the genetic information directly *in vivo* into the cells of the organs or tissues targeted by the therapy]

At page 5, please delete the paragraph at line 5-13, replace with the following:

-- The nucleic acid sequence entering into the composition of the biological material of the invention includes:

[-]• at least one therapeutic antibody gene, [or] which is to say a gene coding for a [virgin] native, unmodified [,and therefore natural] antibody therefore natural, or an antibody fragment, such as Fab or $F(ab)_2$ or ScFv fragments, or an antibody derivative such as a chimerical antibody or antibody or antibody fragment fused to an effector substance such as a toxin or hormone;

[-]• at least one element guaranteeing the expression of the preceding gene; promoter sequences of the transcription placed upstream of the antibody gene and controlling its expression in the cells not naturally producing antibodies.--

At page 12, after the paragraph ending on line 22, please insert the following:

--BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 (panels 1a and 1b) provides the nucleotide sequence and the amino acid sequence of variable portions of the light chain of the Tg10 antibody;

Figure 2 (panels 1a and 1b) provides the nucleotide sequence and the amino acid sequence of variable portions of the heavy chain of the Tg10 antibody;

Figure 3 depicts the cDNA of the light chain and heavy chain of the Tg10 antibody in the pLXPXSN retroviral vector cloned either on both sides of the IRES sequence of the poliovirus to form the PM130 vector, or individually upstream of the IRES sequence to form the PM117 and PM124 vectors.--

Please insert the sequence listing pages 1-4 at the end of the specification.

In the Claims:

Please cancel claims 1, 4, 5, 11, 13, 14, 20, 21 and 31 and insert new claims 32-42.

Second Edition

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whereas others are directed to an organelle inside the cell. Proteins synthesized by the rough ER also emerge as integral membrane proteins in the plasma membrane and intracellular membranes.

SIGNAL SEQUENCES ENABLE SECRETORY PROTEINS TO CROSS THE ENDOPLASMIC RETICULUM MEMBRANE

Studies of the protein-synthesizing activities of ribosomes in cell-free systems provided the answer to the first of these questions. Free ribosomes from the cytosol were isolated and then added to rough ER membranes that had been stripped of their ribosomes. This reconstituted system actively synthesized secretory proteins when presented with the appropriate mRNAs and other soluble factors. Likewise, ribosomes derived from the rough ER were fully active in synthesizing proteins that are normally released into the cytosol. Furthermore, there were no detectable structural differences between free ribosomes and ribosomes derived from the rough ER. *Thus, membrane-bound ribosomes and free ribosomes are intrinsically the same. Whether a particular ribosome is free or attached to the rough ER depends only on the kind of protein it is making.*

What then is the marker on a nascent protein that determines whether its associated ribosome is to be free in the cytosol or bound to the ER membrane? In 1970, David Sabatini and Günter Blobel postulated that *the signal for attachment is provided by a sequence of amino acid residues near the amino-terminus of the nascent polypeptide chain.* This *signal hypothesis* (Figure 29-42) was soon supported by the finding of Cesar Milstein and George Brownlee that an immunoglobulin chain synthesized in vitro by free ribosomes contained an amino-terminal sequence of twenty residues that was absent from the mature protein synthesized in vivo. Blobel then found that all of the major secretory proteins of the pancreas contain amino-terminal extensions of some twenty residues when synthesized in vitro by free ribosomes. The signal sequences of many secretory proteins are now

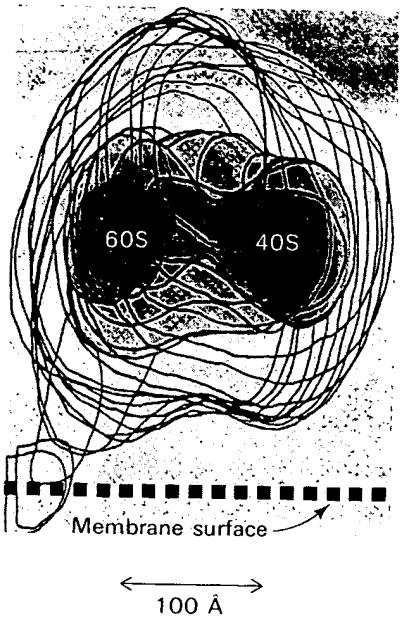


Figure 29-41
Low-resolution image of a membrane-bound ribosome. This image was reconstructed from a series of electron micrographs of ordered arrays of ribosomes at different tilt angles. [After a diagram kindly provided by Dr. Nigel Unwin.]

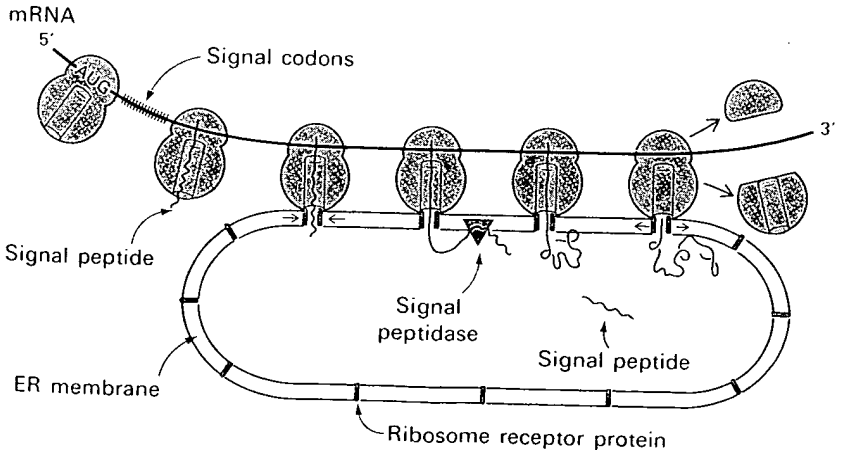


Figure 29-42
Signal hypothesis for the biosynthesis of secretory and membrane proteins. In this model, the amino-terminal sequence (shown in red) of the nascent polypeptide chain binds the ribosome to the ER membrane. The signal sequence is then excised by a peptidase on the luminal side of the ER. [After G. Blobel. In *International Cell Biology*, B. R. Brinkley and K. R. Porter, eds. (Rockefeller University Press, 1977), p. 318.]

known. They range in length from about fifteen to thirty residues and contain a high proportion of nonpolar residues (Figure 29-43).

H_3^+N-Met-Arg-Ser-Leu-Leu-Ile-Leu-Val-Leu-Cys-
-Phe-Leu-Pro-Leu-Ala-Ala-Leu-Gly⟩Gly-Lys-
Prelysozyme

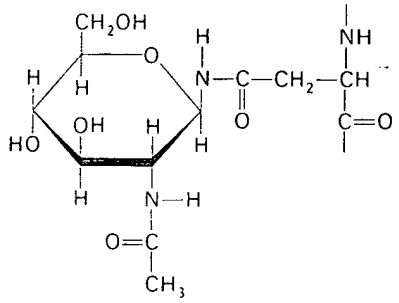
H_3^+N-Met-Lys-Trp-Val-Thr-Phe-Leu-Leu-Leu-Leu-
-Phe-Ile-Ser-Gly-Ser-Ala-Phe-Ser⟩Arg-
Preproalbumin

Figure 29-43
Signal sequences of two secretory proteins. Hydrophobic residues are shaded yellow. The cleavage site is marked in red.

Hydrophobic signal sequences probably adopt conformations that are recognized by channel proteins in the ER membrane. *It seems likely that the nascent polypeptide chain is actively threaded through a tunnel in the ER membrane as it is being synthesized.* The signal sequence is then cleaved by a peptidase on the luminal side of the ER (see Figure 29-42). Nascent chains destined to become integral membrane proteins probably contain specific sequences that block the transfer of the polypeptide across the ER membrane before the carboxyl-terminal end is reached. In contrast, the entire polypeptide chain is transported across the ER membrane in the case of secretory proteins.

A key feature of the signal sequence mechanism is that transfer of the polypeptide across the ER membrane is coupled to translation. *However, some proteins can cross membranes after their synthesis is finished.* For example, most mitochondrial and chloroplast proteins are encoded by nuclear genes and synthesized by free ribosomes. These proteins are released into the cytosol and then traverse the organelle membrane. Transport of these proteins is clearly *posttranslational* rather than cotranslational. It is interesting to note that these mitochondrial and chloroplast proteins, like secretory proteins, contain N-terminal sequences that are removed soon after their emergence through the membrane.

GLYCOPROTEINS ACQUIRE THEIR CORE SUGARS FROM DOLICHOL DONORS IN THE ENDOPLASMIC RETICULUM



***N*-Acetylglucosamine linked to an asparagine residue by an *N*-glycosidic bond**

Nearly all proteins synthesized by ribosomes bound to the ER acquire covalently attached carbohydrate units. In contrast, soluble proteins synthesized by free ribosomes in the cytosol are almost always devoid of carbohydrate. As mentioned earlier, sugar units may orient glycoproteins in membranes (p. 222). In addition, carbohydrate groups may participate in determining the destination of a glycoprotein. A typical glycoprotein contains one or a few oligosaccharide units linked to asparagine side chains by *N*-glycosidic bonds. Less common is the attachment of sugars to serine and threonine side chains by *O*-glycosidic bonds. The sugar directly bonded